S PONTANEOUS bacterial peritonitis is a common and severe complication in patients with cirrhosis and ascites. It probably originates with the passage of bacteria from the intestinal lumen to the systemic circulation and then to the ascitic fluid. Although the concentration of bacteria in ascitic fluid is low, the inflammatory response, as estimated by the concentration of polymorphonuclear leukocytes and cytokines (tumor necrosis factor α and interleukin-6) in ascitic fluid and blood, is very intense.

In one third of patients with spontaneous bacterial peritonitis, renal impairment develops despite treatment of their infection with non-nephrotoxic antibiotics. This deterioration of renal function is the most sensitive predictor of in-hospital mortality. Renal impairment occurs in patients with the highest concentrations of cytokines in plasma and ascitic fluid and is associated with marked activation of the renin–angiotensin system. It is considered to be caused by a decrease in effective arterial blood volume as a result of the infection.

We conducted a study to determine whether plasma volume expansion with albumin could prevent the impairment of renal function and reduce mortality in patients with spontaneous bacterial peritonitis.

METHODS

Patients

A total of 199 consecutive patients with cirrhosis who had spontaneous bacterial peritonitis and who were admitted between November 1995 and September 1997 to seven university hospitals were evaluated for inclusion in the study. The study was approved by the investigational review board at each hospital, and patients gave written informed consent to participate. Inclusion criteria were a polymorphonuclear-cell count in the ascitic fluid of more than 250 per cubic millimeter, in the absence of findings suggestive of secondary peritonitis (10 ml of blood and ascitic fluid was inoculated in blood-culture bottles at the patient’s bedside); an age between 18 and 80 years; no antibiotic treatment within one week before the diagnosis of spontaneous bacterial peritonitis (except for prophylactic treatment with norfloxacin); the absence of other infections, shock, gastrointestinal bleeding, ileus, grade 3 or 4 hepatic encephalopathy on the Conn and Lieberthal scale; cardiac failure, findings suggestive of organic nephropathy (proteinuria, hematuria, or abnormal findings on renal ultrasonography), human immunodeficiency virus infection, and any disease (e.g., advanced neoplasia) that could affect the short-term prognosis; a serum creatinine level of no more than 3 mg per deciliter (265 µmol per liter); and the absence of potential causes of dehydration (such as diarrhea or an intense response to diuretic treatment) within one week before the diagnosis of peri-

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Renal Function

The main end points of the study were the development of renal impairment and mortality. The end point chosen to calculate the sample size was the development of renal impairment. Assuming that renal impairment develops in approximately 30 percent of patients with spontaneous bacterial peritonitis that is treated with cefotaxime, a minimum of 50 patients per group was required to allow detection of a difference of 25 percent between the two groups in the proportion of patients with this complication during hospitalization, with a two-sided type I error rate of 5 percent and a type II error rate of 20 percent. The final analysis was conducted on an intention-to-treat basis. Comparisons between groups were performed with use of the chi-square test or Fisher’s exact test for categorical data and Student’s t-test for continuous data. The same univariate analyses were also used to identify factors predicting the development of renal impairment and in-hospital mortality. These factors were identified from a list of 28 variables that included information from the medical history and base-line clinical evaluation and laboratory tests, as well as the treatment assignment. Variables that reached statistical significance in univariate analyses were subsequently included in multivariate analyses (by stepwise logistic regression) in order to identify independent predictors of the two main end points.

The analysis of the results was verified by a central review committee at the Hospital Clinic of Barcelona. Results are presented as means ±SE. All reported P values are two-tailed. Values of less than 0.05 were considered to indicate statistical significance.

RESULTS

Base-Line Characteristics of the Patients

There were no significant differences between the groups in clinical and laboratory data at enrollment (Table 1). All the patients in the cefotaxime-plus-albumin group received the scheduled doses of albumin except for the two patients who were withdrawn from this group because they did not meet the inclusion criteria. There were no adverse effects of the albumin infusion. One patient in the cefotaxime group was treated with intravenous ofloxacin because of a previous allergic reaction to cephalosporins.

Renal Function

The infection resolved in most of the patients in each group. Despite a similar rate of resolution of infection, the incidence of renal impairment was markedly lower among the patients treated with cefotax-
TABLE 1. BASE-LINE CHARACTERISTICS OF THE 126 PATIENTS ACCORDING TO THE ASSIGNED TREATMENT.*

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>CFOTAXIME (N=63)</th>
<th>CFOTAXIME PLUS ALBUMIN (N=63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>62±1</td>
<td>60±1</td>
</tr>
<tr>
<td>Sex — M/F</td>
<td>38/25</td>
<td>43/20</td>
</tr>
<tr>
<td>Alcoholic cirrhosis — no. (%)</td>
<td>19 (30)</td>
<td>18 (29)</td>
</tr>
<tr>
<td>Hepatocellular carcinoma — no. (%)</td>
<td>7 (11)</td>
<td>10 (16)</td>
</tr>
<tr>
<td>Hepatic encephalopathy — no. (%)</td>
<td>15 (24)</td>
<td>13 (21)</td>
</tr>
<tr>
<td>White-cell count — per mm³</td>
<td>9221±814</td>
<td>7883±560</td>
</tr>
<tr>
<td>Ascitic-fluid polymorphonuclear cells — per mm³</td>
<td>4228±750</td>
<td>5223±1541</td>
</tr>
<tr>
<td>Serum bilirubin — mg/dl</td>
<td>6.2±1</td>
<td>4±1</td>
</tr>
<tr>
<td>Serum albumin — g/dl</td>
<td>2.5±0.1</td>
<td>2.7±0.1</td>
</tr>
<tr>
<td>Prothrombin time — % of control</td>
<td>58±2</td>
<td>55±2</td>
</tr>
<tr>
<td>Child–Pugh score†</td>
<td>10±0.2</td>
<td>10±0.2</td>
</tr>
<tr>
<td>Renal failure — no. (%)</td>
<td>28 (44)</td>
<td>25 (40)</td>
</tr>
<tr>
<td>Diuretic treatment — no. (%)</td>
<td>41 (65)</td>
<td>45 (71)</td>
</tr>
<tr>
<td>Spironolactone — mg/day</td>
<td>73±5</td>
<td>81±6</td>
</tr>
<tr>
<td>Furosemide — mg/day</td>
<td>19±1</td>
<td>18±2</td>
</tr>
<tr>
<td>Previous prophylactic treatment with norfloxacin — no. (%)</td>
<td>5 (8)</td>
<td>6 (10)</td>
</tr>
<tr>
<td>Isolated organisms — no. (%)‡</td>
<td>36 (57)</td>
<td>32 (51)</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>22</td>
<td>20</td>
</tr>
<tr>
<td>Other gram-negative bacilli</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Other bacteria</td>
<td>8</td>
<td>5</td>
</tr>
</tbody>
</table>

*Plus–minus values are means ±SE. No significant differences were found between the two groups in any of the characteristics. To convert the values for serum bilirubin to micromoles per liter, multiply by 17.1.

†The Child–Pugh score (range, 5 to 15, where 5 indicates good liver function and 15 indicates poor liver function) was calculated on the basis of the presence and degree of hepatic encephalopathy, the presence and degree of ascites, the serum bilirubin level, the serum albumin level, and the prothrombin time.

‡Organisms were isolated from ascitic fluid or blood.

TABLE 2. CLINICAL OUTCOME ACCORDING TO THE ASSIGNED TREATMENT.*

<table>
<thead>
<tr>
<th>OUTCOME VARIABLE</th>
<th>CFOTAXIME (N=63)</th>
<th>CFOTAXIME PLUS ALBUMIN (N=63)</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resolution of infection — no. (%)‡</td>
<td>59 (94)</td>
<td>62 (98)</td>
<td>0.36</td>
</tr>
<tr>
<td>Duration of antibiotic therapy — days</td>
<td>6±1</td>
<td>5±1</td>
<td>0.48</td>
</tr>
<tr>
<td>Paracentesis for ascites after resolution of infection — no. (%)‡</td>
<td>16 (25)</td>
<td>14 (22)</td>
<td>0.83</td>
</tr>
<tr>
<td>Hospital stay — days</td>
<td>13±1</td>
<td>14±1</td>
<td>0.48</td>
</tr>
<tr>
<td>Renal impairment — no. (%)</td>
<td>21 (33)</td>
<td>6 (10)</td>
<td>0.002</td>
</tr>
<tr>
<td>Death — no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In hospital§</td>
<td>18 (29)</td>
<td>6 (10)</td>
<td>0.01</td>
</tr>
<tr>
<td>At three months¶</td>
<td>26 (41)</td>
<td>14 (22)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*Plus–minus values are means ±SE.

†The infection resolved with the initial cefotaxime therapy in 55 of the 63 patients (84 percent) in the cefotaxime group and in 57 of the 63 patients (90 percent) in the cefotaxime-plus-albumin group. In the other patients, the infection resolved after modification of the antibiotic therapy.

‡These patients required at least one therapeutic paracentesis for the management of ascites.

§The causes of in-hospital death were combined liver and renal failure (13 patients in the cefotaxime group and 5 in the cefotaxime-plus-albumin group), massive gastrointestinal hemorrhage (2 patients in the cefotaxime group and 1 in the cefotaxime-plus-albumin group), septic shock (2 patients in the cefotaxime group), and liver failure (1 patient in the cefotaxime group).

¶Seven patients (four in the cefotaxime group and three in the cefotaxime-plus-albumin group) were lost to follow-up after discharge from the hospital. The three-month mortality rates were calculated as the number of known deaths at this time divided by the total number of enrolled patients in each group.

Mortality

Mortality during hospitalization was significantly lower among patients treated with cefotaxime and albumin than among those treated with cefotaxime alone (10 percent vs. 29 percent, P=0.01) (Table 2). Independent predictors of in-hospital mortality were the blood urea nitrogen level (P=0.001), serum bilirubin level (P=0.01), and prothrombin time with a base-line serum bilirubin level of at least 4 mg per deciliter (68 µmol per liter) was 48 percent (14 of 29 patients) in the cefotaxime group, as compared with 12 percent (3 of 25 patients) in the cefotaxime-plus-albumin group, regardless of the serum creatinine level. Corresponding results in patients with a serum bilirubin level of less than 4 mg per deciliter and a serum creatinine level of at least 1 mg per deciliter were 32 percent (6 of 19 patients) and 14 percent (3 of 21 patients), respectively. The incidence of renal impairment among patients with a serum bilirubin level of less than 4 mg per deciliter and a serum creatinine level of less than 1 mg per deciliter was very low in both treatment groups (7 percent and 0 percent in the cefotaxime and cefotaxime-plus-albumin groups, respectively).
The impairment of renal function is an important clinical event in patients with cirrhosis and spontaneous bacterial peritonitis. The incidence of renal impairment was significantly lower among patients treated with cefotaxime and albumin than among patients treated with cefotaxime alone. In-hospital mortality in the group of patients treated with cefotaxime (29 percent) was significantly lower among patients treated with cefotaxime alone. In-hospital mortality in the group treated with cefotaxime and albumin was only 10 percent. This reduction in mortality occurred primarily in patients who did not receive albumin. No significant differences in arterial pressure were found between the two groups of patients at any time during the study (Table 3).

There was a close relation between the development of renal impairment and the increase in plasma renin activity (Fig. 1B). Plasma renin activity increased markedly in the patients in whom renal impairment developed but did not change significantly in the patients without renal impairment.

**DISCUSSION**

We found that the administration of albumin prevents renal impairment and reduces mortality in patients with cirrhosis and spontaneous bacterial peritonitis. The incidence of renal impairment was significantly lower among patients treated with cefotaxime and albumin than among patients treated with cefotaxime alone. In-hospital mortality in the group of patients treated with cefotaxime (29 percent) was similar to that reported in most studies.2-7 By contrast, in-hospital mortality in the group treated with cefotaxime and albumin was only 10 percent. This rate is slightly higher than that reported for patients hospitalized for the treatment of ascites.18,21 In multivariate analyses, treatment (cefotaxime and albumin or cefotaxime alone) was an independent predictor of renal impairment and in-hospital mortality.

The impairment of renal function is an important clinical event in patients with cirrhosis and spontaneous bacterial peritonitis. In our study, nonreversible renal impairment developed in one third of the patients treated with cefotaxime alone, and in most patients who did not receive albumin. No significant differences in arterial pressure were found between the two groups of patients at any time during the study (Table 3).

There was a close relation between the development of renal impairment and the increase in plasma renin activity (Fig. 1B). Plasma renin activity increased markedly in the patients in whom renal impairment developed but did not change significantly in the patients without renal impairment.

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cases it was progressive, despite rapid resolution of the infection.

The pathogenesis of renal impairment associated with spontaneous bacterial peritonitis is probably hemodynamic. Patients with cirrhosis and ascites have a circulatory dysfunction characterized by arteriolar vasodilatation, hypotension, high cardiac output, decreased effective arterial blood volume, homeostatic activation of the renin–angiotensin and sympathetic nervous systems, and increased circulating levels of arginine vasopressin and endothelin.22-24 Because these systems act as renal vasoconstrictors, renal perfusion and glomerular filtration are maintained in these patients by compensatory activation of renal vasodilators, especially prostaglandins,25,26

Patients with cirrhosis and spontaneous bacterial peritonitis have many of the features of the sepsis syndrome, including blood cultures that are positive for bacteria1,14 and high levels of vasoactive cytokines.10,11 The sepsis syndrome is also associated with arterial vasodilatation, impairment of circulatory function, and activation of neurohumoral vasoconstrictor systems.27-29 Therefore, the high frequency and severity of renal impairment after the onset of spontaneous bacterial peritonitis are probably due to the combination of circulatory failure induced by infection and circulatory failure already present as a consequence of cirrhosis. This combined effect probably overcomes the compensatory action of renal vasodilators and thus leads to decreases in renal perfusion and the glomerular filtration rate. Our finding that renal impairment is associated with additional stimulation of the already activated renin–angiotensin system is consistent with this hypothesis. The absence of a change in arterial pressure does not rule out this possibility, because a reduction in arterial pressure might have been offset by the vasoconstrictor activity of the renin–angiotensin system.

The development of circulatory dysfunction, renal impairment, and mortality were found to be strongly related in patients with spontaneous bacterial peritonitis. Whether circulatory dysfunction and subsequent renal impairment contribute to the poor prognosis for these patients is unknown. It could be that both

Figure 1. Mean (±SE) Plasma Renin Activity on Days 0, 3, 6, and 9. Panel A shows plasma renin activity in patients treated with cefotaxime plus albumin and in patients treated with cefotaxime alone. Panel B shows plasma renin activity in patients in whom renal impairment did not develop and in those in whom it did. Plasma renin activity was measured by radioimmunoassay.28 The normal mean value in healthy subjects is 1.4±0.4 ng per milliliter per hour.28 Asterisks indicate P<0.001, daggers indicate P=0.005, and the double dagger indicates P=0.02 for the comparison between patients who received cefotaxime plus albumin and those who received cefotaxime alone (Panel A) or for the comparison between patients without renal failure and those with it (Panel B).
conditions are only markers of terminal liver failure and do not contribute directly to the poor outcome. Alternatively, the vasconstrictor mechanisms that are activated as a homeostatic response to circulatory dysfunction may be harmful in patients with cirrhosis: as discussed previously, the overactivity of neurohumoral vasconstrictors may induce renal hypoperfusion by acting on the renal circulation.3,20,23 There is increasing evidence, however, that vasconstrictors may enhance intraperitoneal vascular resistance by acting on vascular smooth-muscle cells or stellate cells in the hepatic circulation.31-33 This effect would reduce hepatic blood flow and aggravate portal hypertension and liver failure. The deleterious effects of circulatory dysfunction on the kidneys and liver may thus account for the poor outcome in patients with spontaneous bacterial peritonitis.

A close relation between impaired circulatory function and mortality has also been reported in patients with cirrhosis who were treated by large-volume paracentesis.20 In such patients, impaired circulatory function is associated with an increase in portal pressure.24 Thus, the most likely explanation for the reduced rate of early mortality in patients who are treated with albumin is that such treatment prevents circulatory dysfunction (i.e., maintaining the effective arterial blood volume) and the subsequent activation of vasconstrictor systems. However, the possibility that the beneficial effects of albumin involve mechanisms other than those related to plasma expansion cannot be ruled out.

Intravenous albumin is expensive (approximately $5 per gram in Spain) and has limited availability in some settings. Therefore, studies should be performed to determine whether treatment of spontaneous bacterial peritonitis with lower doses of albumin or with artificial plasma expanders, which are less expensive, would have similar beneficial effects on renal function and survival.

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